

New strategies in the search of antipsychotic drugs

Schizophrenia is a chronic, severe, and disabling brain disorder characterized by a profound disruption of perception, cognition, and emotion. The condition affects approximately 1% of the population and is thought to be the result of genetic vulnerability and environmental influences. The symptoms of schizophrenia fall into three main categories, i.e. positive symptoms (hallucinations, delusions), negative symptoms (apathy, lack of emotion) and cognitive symptoms (problems with attention, certain types of memory, and executive functions). Antipsychotic medications available effectively alleviate the positive symptoms of schizophrenia. However, negative symptoms and cognitive deficits remain poorly treated and are considered to belong to a core syndrome in schizophrenia. For this reason, investigators are developing more effective medications and using new research tools to understand the causes of schizophrenia and to find better ways to prevent and treat it.

The present issue provides a state of the art review of some of these new pharmacological approaches in this rapidly expanding area. Mailman and Murthy provide an historical overview of antipsychotic medication and describe functional selectivity at D₂ dopamine receptors as a novel mechanism of antipsychotic drug action [1]. The new concept of functional selectivity posits that a ligand may inherently produce a mix of effects through a single receptor depending on the effector pathway coupled to that receptor [2]. Thus, it is conceivable that a ligand or drug might target not the receptor alone, but a receptor-directed signaling complex. With regard to antipsychotic drug action, it was envisaged that if dopamine D₂ autoreceptors could be preferentially activated with a dopamine agonist, then dopaminergic transmission might be diminished, which could lead to a functional dopamine antagonist-like effect. In theory, therefore, a low dose of a full agonist could be used to decrease dopamine release, thereby causing benefit in schizophrenia. López-Gil and co-workers have studied the cortical glutamatergic and serotonergic transmission in an animal model of schizophrenia based on NMDA hypofunction [3]. The results suggest that serotonergic transmission in the prefrontal cortex is regulated by the concurrent participation of multiple monoamine receptors, whereas glutamatergic transmission is strongly dependent on dopamine D₂-like receptor activation. Thus, although further testing of newer antipsychotics is warranted, it seems that so-called atypical antipsychotic drugs are able to block increases in cortical glutamate and serotonin elicited by a NMDA

receptor antagonist. However, classical antipsychotics appear to block only the increased glutamatergic transmission. Based on a large study with selective agonist and antagonist compounds for which antipsychotic drugs possess some affinity, these authors propose that dopamine D2 receptor antagonists would increase cortical GABAergic inhibition whereas other monoaminergic compounds (5-HT_{2A} and α_1 -adrenergic antagonists as well as 5-HT_{1A} agonist) would be helpful in reducing an excessive excitatory transmission in the prefrontal cortex. McCreary and Jones report on the beneficial effects of serotonin 5-HT_{1A} receptor agonists in the alleviation of symptoms of schizophrenia [4]. There is growing interest in 5-HT_{1A} receptors as potential targets for antipsychotic drug action [5]. Indeed, a series of studies using the 5-HT_{1A} partial agonists tandospirone and buspirone have reported a modest ability of these agents to improve some domains of cognition in patients receiving typical or atypical antipsychotic drugs. However, it remains to be determined whether these compounds act on presynaptic or postsynaptic 5-HT_{1A} receptors. Postsynaptic 5-HT_{1A} receptors are highly expressed in the hippocampus, frontal cortex, entorhinal cortex and the amygdala, all of which have been implicated in various features of schizophrenia. Preclinical studies have evidenced that 5-HT_{1A} receptors located in the prefrontal cortex seem to be crucial for the ability of atypical (but not classical) antipsychotics to increase cortical dopamine release, an effect potentially involved in the improvement of negative symptoms and cognitive dysfunction in schizophrenia. Tsai and co-workers [6] have dealt with the importance of increasing NMDA receptor mediated glutamatergic transmission in the treatment of schizophrenia [7]. This therapy is directly based upon the hypothesis that the illness is caused by an impaired glutamatergic transmission at NMDA receptors. These authors report a meta-analysis of the efficacy and side effects, in schizophrenia treatment, of agents that enhance NMDA receptor neurotransmission via their action at the NMDA receptor-associated glycine (Gly) site. Overall, although NMDA-enhancing agents as a group show promise in improving some of the symptoms of schizophrenia when added to stable antipsychotic treatment, they do not seem to be an option as a sole pharmacological treatment of the illness. Finally, Hajós and Rogers provide a timely review of α_7 nicotinic acetylcholine receptors [8], which is an important area of potential therapeutics in schizophrenia because α_7 nicotinic partial agonists have been shown to exhibit pro-cognitive and antipsychotic actions [9]. The high level of expression of this receptor within the limbic circuitry, including hippocampus and prefrontal cortex is in line with their purported involvement in cognitive functions. The stimulation of α_7 nicotinic acetylcholine receptors by agonists or positive allosteric modulators is believed to

activate impaired GABA transmission, thus leading to a restitution of gamma-frequency oscillations. However, a considerable advance in this field has been done in the preclinical setting and there are only very limited data on the cognitive effects of such compounds in humans.

Overall the contributions of this special issue provide a valuable opportunity for a multidisciplinary discussion of approaches to increase our knowledge of the complex pharmacology of antipsychotic medications.

All the papers in this issue have been subjected to a peer review process. Thanks are given to the Editorial Board and referees who have helped to produce this issue.

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